REMARKS

Introductory Matter

Applicants wish to thank Examiner Rao for discussing the September 30, 2005 Office Action with applicants' representative, Mr. Roise, by telephone on March 1, 2005. In that discussion, the Examiner and applicants' representative discussed the amendments presented herein. The Examiner indicated that these amendments would be allowable.

Claim Amendments

Applicants have amended claim 11 to specify that R^4 includes hydrogen. Support for this amendment appears, e.g., in compound 18 at page 18 of the specification as filed and in original claim 20.

Applicants have amended claims 22-25 and 30 to delete reference to the terms "prevent" and "preventing".

Applicants have amended claims 22, 24, and 30 to delete reference to certain diseases.

Applicants have amended claim 22 to recite a method of treating myocardial ischemia and renal ischemia. Support for this amendment appears, e.g., in the specification at page 22, lines 6-9, and in claim 30 as originally filed. Applicants have also amended claim 22 to recite a method of treating rheumatoid arthritis, inflammatory bowel disease, ulcerative colitis, and Crohn's disease. Support for this amendment appears, e.g., in the specification at page 20, line 17 to page 21, line 12, and in claim 24 as originally filed.

Applicants have amended claim 25 to correct a minor grammatical error.

Applicants have canceled claims 26-29 and 31-33.

The cancellation of subject matter by these amendments is expressly without waiver of applicants' rights to file divisional or continuing applications directed to the canceled subject matter and claiming priority from this application.

None of these amendments adds new matter. Their entry is requested.

Claim Rejections under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 22-33 under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement. According to the Examiner, "the specification, while being enabling for the treatment of arthritis, does not reasonably provide enablement for treating or preventing inflammatory diseases, infectious diseases, proliferative diseases, neurodegenerative diseases, autoimmune diseases, etc." Office Action, page 2.[1] The Examiner contends that the disclosure of p38 inhibition activity in the specification does not adequately enable the scope of claims covering the treatment of the various recited diseases as well as diseases yet to be discovered. The Examiner further contends that no evidence is provided to enable the "prevention" of diseases as encompassed by the instant claims. Applicants traverse.

Applicants disagree that the instant specification does not fully enable the methods of disease treatment and prevention as currently claimed. Solely to expedite prosecution, however, applicants have canceled claims 26-29 and 31-33 and have amended

[1] The Examiner states at page 2 of the Office Action that "reasons provided in the previous office action are incorporated here by reference." Applicants note for the record that there have been no previous office actions in the instant application.

claims 22-25 and 30 to delete reference to the terms "prevent" and "preventing". Applicants have further amended claims 22, 24, and 30 to delete reference to certain diseases. Amended claims 22-25 and 30 are fully enabled by the evidence of record for at least the following reasons.

First, the *in vitro* assays provided at page 19 of the specification are useful for determining that the compounds of the present invention are inhibitors of p38. Applicants will show that p38 inhibitors can provide therapeutic benefits against the claimed diseases.

Second, applicants disagree that because the diseases recited in claims 22-25 and 30 have different mechanisms of action they cannot all be treated by administration of the p38 inhibitors according to the present invention. These diseases are all mediated by cytokines and other inflammatory proteins which are in turn mediated by p38. Specifically, the specification as filed discloses that inhibiting p38 kinase leads to a blockade of the production of IL-1 and TNF. IL-1 and TNF, in turn, stimulate the production of cytokines such as IL-6 and IL-8 (specification page 2, lines 9-14). Thus, inhibiting p38 would lead to a blockade of production of IL-1, TNF, IL-6 and IL-8 and other pro-inflammatory proteins. IL-1, TNF, IL-6, and IL-8 are all involved in various inflammatory and immune responses. As will be discussed in more detail below, the diversity of actions of p38 kinase gives rise to a broad range of applications for the p38 inhibitors of the present invention. As disclosed in the specification as filed, p38 has been implicated in a broad array of disease states and target organs.

Third, the documents discussed below establish a link between p38 and several specific diseases, namely, rheumatoid arthritis, endotoxin-induced shock, Crohn's disease, burn-mediated cardiac dysfunction, cardiac hypertrophy, congestive heart failure, pulmonary inflammation, and ischemia. More specifically, Suzuki has confirmed a link between p38 and the inflammatory cytokines IL-6 and IL-8.[2] Suzuki showed that treatment of rheumatoid synovial fibroblasts with a p38 inhibitor led to specific suppression of IL-6 and IL-8 production, thereby demonstrating that "p38 MAP kinase is involved in the induction of inflammatory cytokines" (Suzuki, p. 26). Accordingly, p38 inhibitors may be effective for the treatment of rheumatoid arthritis and other inflammatory and autoimmune diseases in which inflammatory cytokines play a crucial role.

Badger I also demonstrates that inhibition of p38 inhibits production of inflammatory cytokines.[3] Specifically, Badger I supports a correlation between inhibition of p38 and inhibition of the pro-inflammatory protein TNF-α (Badger I, p. 1455). Badger I reports the efficacy of a p38 inhibitor in a variety of TNF-α-mediated animal models of inflammatory diseases that arise by both autoimmune and infectious pathways. Administration of a p38 inhibitor reduced joint edema by 72 and 45% in the mouse collagen-induced arthritis

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[2] Suzuki, M. et al., "The Role of p38 Mitogen-Activated Protein Kinase in IL-6 and IL-8 Production from the TNF-α- or IL-1β-stimulated Rheumatoid Synovial Fibroblasts," FEBS Letters, 465, pp. 23-27 (2000) ("Suzuki", Exhibit 2).

[3] Badger, A.M. et al., "Pharmacological Profile of SB 203580, a Selective Inhibitor of Cytokine Suppressive Binding Protein/p38 Kinase, in Animal Models of Arthritis, Bone Resorption, Endotoxin Shock and Immune Function," J. Pharmacol. Exp. Ther., 279, pp. 1453-1461 (1996) ("Badger I", Exhibit 3).

model; reduced paw inflammation in the rat adjuvant arthritis model; inhibited bone resorption in the fetal rat long bone assay; and improved mouse survival in a model of endotoxin-induced shock (Badger I, p. 1459-60).

Badger II further supports the link between p38 and inflammatory cytokine synthesis.[4] As discussed in Badger II, "inhibition of p38 MAP kinase and subsequent inhibition of the synthesis of a number of important proinflammatory proteins has been identified as the primary mechanism contributing to the antiinflammatory activity of [p38 inhibitors]" (Badger II, p. 181). Importantly, the p38 pathway is "commonly associated with the early stages of host response to injury and infection" (Badger II, p. 181). Badger II observed significant antiinflammatory activity in an aggressive arthritis model of Lewis rats treated either prophylactically or therapeutically with a p38 inhibitor. Rats treated at 60 mg/kg showed 73% inhibition of paw edema and 53% normalization of bone mineral density (Badger II, p. 182). A p38 inhibitor has thus been demonstrated to have antiinflammatory effects and to protect against bone damage (Badger II, p. 182).

Humans with Crohn's Disease ("CD") have responded favorably to treatment with a p38 inhibitor in a clinical trial reported by Hommes.[5] CD is a chronic inflammatory

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[4] Badger, A.M. et al., "Disease-Modifying Activity of SB 242235, a Selective Inhibitor of p38 Mitogen-Activated Protein Kinase, in Rat Adjuvant-Induced Arthritis," Arthritis Rheum., 43, pp. 175-183 (2000) ("Badger II", Exhibit 4).

[5] Hommes, D. et al., "Inhibition of Stress-Activated MAP Kinases Induces Clinical Improvement in Moderate to Severe Crohn's Disease," Gastroenterology, 122, pp. 7-14 (2002) ("Hommes", Exhibit 5).

disease that arises via an autoimmune response (Hommes, p. 7). Hommes treated 12 patients suffering from moderate to severe CD with a p38 inhibitor and reported a corresponding decrease in TNF-α production in addition to significant clinical effects (Hommes, p. 13). Thus, a correlation between p38 inhibition and the treatment of inflammatory and autoimmune diseases, including CD, has been demonstrated.

Ballard-Croft further supports the finding that p38 acts through the activation of inflammatory cytokines such as TNF-α.[6] Specifically, Ballard-Croft has linked p38 inhibition to the inhibition of cardiomyocyte secretion of TNF-α and the prevention of burn-mediated cardiac dysfunction (Ballard-Croft, p. H1978). These findings indicate that administration of a p38 inhibitor interrupts postburn inflammation by targeting cardiac myocytes (Ballard-Croft, p. H1978).

Shimamoto has confirmed a correlation between p38, IL-1 and cardiac hypertrophy and congestive heart failure.[7] As discussed in Shimamoto, treatment of Dahl salt-sensitive rats with a p38 inhibitor "suppressed IL-1β production" and "prevented progression of cardiac hypertrophy and congestive heart failure" (Shimamoto, p. 1415).

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[6] Ballard-Croft, C. et al., "Role of p38 Mitogen-Activated Protein Kinase in Cardiac Myocyte Secretion of the Inflammatory Cytokine TNF-α," Am. J. Physiol. Heart Circ. Physiol., 280, pp. H1970-H1981 (2001) ("Ballard-Croft", Exhibit 6).

[7] Shimamoto, A. et al., "Inhibition of p38 Mitogen-Activated Protein Kinase Suppresses Interleukin-1β-Expression and Prevents Progression of Cardiac Hypertrophy and Congestive Heart Failure in Rats," American Heart Association Annual Meeting (2000) ("Shimamoto", Exhibit 7).

The anti-inflammatory effects of p38 have also been shown to occur in the absence of generalized immunosupression, where, for example, p38 exerts an effect on inflammatory cytokines via a signal transduction pathway. Nick[8] showed that administration of a p38 inhibitor modulated neutrophil influx in pulmonary inflammation (Nick, p. 2159). Specifically, inhibition of p38 in a murine model of LPS-induced lung inflammation resulted in a loss of neutrophil migration due to a reduced neutrophil chemotaxic response (Nick, p. 2158).

p38 may also attenuate this signaling cascade in addition to its inflammatory effects. Legos has shown a p38 inhibitor to exhibit a neuroprotective effect through direct effects on ischemic brain cells.[9] p38 is present in the brain "in a wide variety of cell types including neurons, astrocytes, endothelial cells and leukocytes" (Legos, p. 74). p38 activation in the brain is an early response to the cellular stresses of severe focal ischemia, focal stroke, and myocardial/ischemia reperfusion injury (Legos, p. 75). Legos demonstrates that spontaneously hypertensive rats treated with 15 mg/kg of a p38 inhibitor 1 hour pre- and 6 hours post-middle cerebral artery occlusion showed significant neuroprotection, including behavioral improvements and a 48% reduction in infarct volume (Legos, p. 73). Thus, Legos supports a correlation between p38 and neurodegenerative diseases.

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[8] Nick, J.A. et al., "Role of p38 Mitogen-Activated Protein Kinase in a Murine Model of Pulmonary Inflammation," J. Immunol., 164, pp. 2151-2159 (2000) ("Nick", Exhibit 8).

[9] Legos, J.J. et al., "SB 239063, a Novel p38 Inhibitor, Attenuates Early Neuronal Injury Following Ischemia," Brain Research, 892, pp. 70-77 (2001) ("Legos", Exhibit 9).

Barancik further supports the finding that inhibition of p38 protects against ischemic injury.[10] As discussed in Barancik, "p38-MAPK is part of a pathway accelerating cell death" (Barancik, pp. 481-482). Administration of a p38-specific inhibitor before and during myocardial ischemia protected pig myocardium against ischemic cell death (Barancik, p. 480). Therefore, Barancik further supports the action of p38 via a signaling cascade rather than through inflammatory effects.

In sum, the documents of record have established a link between p38 and various disease states via diverse mechanisms. They also demonstrate that p38 inhibition has in vivo effects in animals, including humans, against the diseases recited in amended claims 22-25 and 30.

In view of the teachings of the specification and the knowledge in the art at the time this application was filed, the skilled artisan would be able to practice the claimed methods without undue experimentation and would expect that the claimed methods have the asserted utility. Accordingly, the claimed methods pass muster of Section 112, first paragraph.

Double Patenting

The Examiner has provisionally rejected claims 11-33 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-11, 14, and 20-40 of copending United States Patent Application No. 10/365,719 (Publication

[10] Barancik, M. et al., "Inhibition of the Cardiac p38-MAPK Pathway by SB203580 Delays Ischemic Cell Death," J. Cardiovasc. Pharmacol., 35, pp. 474-484 (2000) ("Barancik", Exhibit 10).

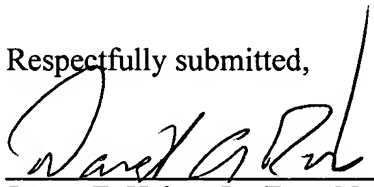
No. 2004/0044002). The Examiner asserts that although the conflicting claims are not identical, they are not patentably distinct from each other because there is a significant overlap between the instantly claimed genus and the genus of the reference claims.

In order to overcome the rejection, applicants stand ready to file a terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) upon notice that the claims are otherwise in condition for allowance.

Conclusion

In view of the above, applicants request that the Examiner enter the amendments, consider the accompanying arguments, withdraw the rejections, and allow the pending claims to pass to issue.

Respectfully submitted,



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